Diffuse Malignant Mesothelioma: A Review

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Diffuse malignant mesothelioma is a signal tumor of asbestos exposure. Mesothelioma incidence has been steadily rising during the past two decades, reflecting the increases in asbestos use during and following World War II. The onset of the disease follows exposure by 25 to 40 years. The dose-response relationship appears to be much lower than that for asbestosis or lung cancer—it is not known whether current levels of exposure will entail a risk for disease 30 years hence. There is no synergistic or additive interaction with smoking for this tumor. Current knowledge indicates that pleural plaques, per se, do not increase the risk for this tumor beyond that of the previous asbestos exposure alone. Durable fibers with high aspect ratios, especially amphiboles, are associated with experimental tumor induction. Treatment modalities including surgical procedures and chemotherapy with doxorubicin and 5-azacytidine offer prospects for palliation.

Diffuse malignant mesothelioma (DMM) has been referred to as a "signal tumor" because of its unique association with occupational or environmental exposure to asbestos.[1] This relationship was first noted over 35 years ago and has been chronicled in more than 175 scientific reports.[2-16] The association with asbestos has now become widely recognized as causal.

The latency period for DMM after the start of asbestos exposure is 25 to 40 years or more. A dramatic increase in the use of asbestos began during World War II and continued over the subsequent three decades; thus, during the 1980's and 1990's, physicians may encounter this tumor more frequently. In contrast to bronchogenic carcinoma, there is no interaction between cigarette smoking and asbestos exposure in the development of this tumor.

A physician suspecting a diagnosis of DMM should take an assiduously thorough occupational history. Most patients are men, reflecting an occupational exposure, but a fleeting or casual exposure in a shipyard, or exposure by working with asbestos in the arts, or by serving an apprenticeship to a lagger may be sufficient to initiate the disease. Contact with asbestos in the environment, such as living or playing near an asbestos factory or tailings dump, or growing up in the household of an asbestos worker who wears asbestos-covered workclothes home from work, may constitute sufficient exposure.

Incidence

The incidence of DMM can be determined from autopsy or pathologic studies, epidemiologic studies and population-based cancer registries. All three sources of data suggest that the incidence of this tumor has increased over the past two decades and that only part of this increase can be explained by a heightened awareness of the disease by physicians and by their improved diagnostic acumen.[17] Furthermore, the increase probably has not peaked because the tumor has such a long latency period. Incidence rates tend to parallel death rates, because patients seldom live longer than 12 to 18 months after diagnosis.

The annual incidence for adults varies between two and three cases per million for men and approximately 0.7 cases per million for women.[18] Theriault and Grand-Bois reported 2.3 to 2.8 cases per million a year in Quebec (where there are asbestos factories, mines and mills), while shipbuilding cities have higher rates, ranging from 5.6 to 8.9 cases in England to 21.4 cases per million a year in Trieste, Italy.[19-21] Autopsy rates have been lower; for example, 0.24 percent from 69,302 autopsies (165 mesotheliomas), representing six series from eight cities from 1950 to 1970.[22] Patients with mesothelioma may selectively be underrepresented in autopsy series, in part because the pathologic diagnosis is notoriously difficult. Reports from pathologists in Canada have shown a 2.5-fold increase of DMM in men in only a

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decade.[18] Population-based cancer registries have also documented an increase; for example, there has been a tenfold rise in incidence over three decades in cases recorded in the Connecticut Tumor Registry.[23]

Three fourths of the patients suffering from this disease are men, presumably reflecting occupational exposures. Eighty percent of the cases affect the pleura with the remainder predominantly located in the peritoneum. A greater proportion of peritoneal DMM has been reported in asbestos insulators, who may have had a heavy exposure in the distant past and presumably swallowed many fibers or had extensive translocation to the peritoneum. Also, more than 80 percent of cases occur during the sixth decade of life or later.

Association With Asbestos

In 1943 Wedler first associated DMM with asbestos exposure, and in 1947 the first report of mesothelioma occurring in the United States was published in the Case Records of the Massachusetts General Hospital.[24,25] Further case reports published in 1953 and 1954 described a pleural and peritoneal mesothelioma with parenchymal asbestosis.[26,27] Scant attention was paid to these case reports associating asbestos with mesothelioma until 1960 when Wagner and associates reported 33 cases of DMM; 32 of the patients had a history of known or potential previous asbestos exposure.[28]

Subsequent case series reports and cohort mortality studies have corroborated the epidemiologic association with exposure to asbestos.[1,29] Case-control studies have consistently found an asbestos exposure relationship with risk for DMM. Selikoff and colleagues have reported that 8 percent of 17,800 asbestos insulators in the United States and Canada whose cases were followed from January 1, 1967, to December 31, 1976, died from DMM.[30] A dose-response relationship has been shown with greater intensity and duration of exposure in an English asbestos factory.[31,32] Whitwell and co-workers extended these observations by determining the light-visible asbestos fiber content of a 1-gram specimen of dried lung using phase contrast microscopy.[33] They found 83 percent of 100 patients suffering from DMM had 100,000 fibers per gram, 80 percent of 100 lung cancer patients had 20,000 fibers per gram and 71 percent of 100 controls had 20,000 fibers per gram.

A history of asbestos exposure can be confirmed in most cases; however, persistence and skill are required in eliciting and interpreting an asbestos exposure. A physician should take a chronological occupational history, giving special consideration to jobs held and possible exposures 20 to 40 years earlier. Asbestos exposures that may cause mesothelioma are encountered in every stage of the production and use of asbestos. Exposures occur in the mining, milling and transportation of raw asbestos. Exposure occurs in asbestos factories in the manufacture of asbestos cement pipe, friction materials, textiles, roofing materials and other products. Construction workers are exposed to asbestos in a variety of occupations—including asbestos insulators, plumbers, welders and electricians. Workers in electrical power plants may be exposed. Many shipyard tradesmen were exposed as "innocent bystanders" while pipecoverers sawed, cut and fitted asbestos into place, or while laborers ripped out asbestos insulation during ship refitting. Asbestos insulation workers exposed in their trade in the past have the greatest relative risk for DMM.[34]

In a prospective study from South Africa, assiduous occupational histories have been obtained in DMM patients.[35] Asbestos exposure criteria included four months of constant exposure to an atmosphere of visible floating asbestos fibers, or four years in room contact with loose fiber not visible in the atmosphere, or three years' residence adjacent to an asbestos production facility. Of 70 consecutive cases of DMM, 69 met these criteria. The series has recently been extended to include more than 130 patients with similar results. Occupational histories are less reliable from family members or relatives of patients and least reliable when obtained from hospital records.[36,37]

A history of household contact with an asbestos worker and hobbies or avocations using asbestos in the home may even be important. During the 1940's and 1950's, when wives washed their husband's contaminated workclothes, they resuspended fibers in the air, possibly exposing the entire household. Anderson and associates reported four cases of DMM from household contact and reviewed 33 other cases where household exposure had been present.[38] A relative risk of ten versus matched, unexposed controls for this type of exposure has been reported utilizing a retrospective case-control technique.[39] Prolonged residence near a shipyard or factory, often 20 to 30 years before onset of the disease, has also been associated with DMM. In 1965 Newhouse reported an occupational or household contact in 40 of 76 cases of DMM versus 9 in matched controls. In addition, 11 of the patients versus 5 controls lived within half a mile of a factory.[40]

Pleural plaques or thickening (or both), despite a single case report, has not been shown to lead directly to DMM.[41] Even though several studies have shown an increased mortality from lung cancer and DMM among asbestos-exposed shipyard workers with pleural disease, the level of risk is still not clear.[42-44] In Finland, where pleural disease is common in the anthophyllite mining region, DMM has not been reported.[45,46]

Clinical Signs and Symptoms

The preeminent symptom of pleural DMM is chest pain; most often it is a persistent, gnawing pain in the involved side. Pleuritic pain is unusual but may occur when the tumor produces a spontaneous pneumothorax. Dyspnea on exertion and weight loss are frequent accompanying symptoms. The major sign is pleural effusion, which may be either serous or serosanguinous. The fluid has a tendency to reaccumulate rapidly following thoracentesis. Pleural effusion is usually the first sign of the tumor and may be present for several months before a diagnosis can be made. Dense pleural thickening is also common, without an effusion being demonstrated radiographically. Results

of blood chemistry studies usually are normal, but the serum lactic dehydrogenase level may be increased.[47] Malignant mesothelioma has also been reported to occur in the pericardium, atrioventricular node and tunica vaginalis testis.[48-51]

Advanced signs and symptoms of DMM include fever, syndrome of inappropriate antidiuretic hormone secretion, arthralgias (usually of fingers, wrists, ankles and shoulders), thrombocytosis and clubbing.[52] Other findings may include cough, hemoptysis, localized edema, Horner's syndrome, vocal cord paralysis, hoarseness, dysphagia and superior vena cava syndrome.[53] The disease advances insidiously with tumor extension involving contiguous structures (rib, lung, diaphragm); metastasis may occur via lymphatics or the bloodstream during later stages of disease. Although seldom manifested clinically, metastatic lesions are frequently found at autopsy. They may involve the contralateral lung, regional lymph nodes, liver, adrenal glands, bone, brain and spinal cord.[54,55] Primary carcinoma and DMM may be discovered simultaneously; it is possible that many of the tumor nodules on the pleura or peritoneum may have arisen de novo rather than from metastasis. Pleural mesotheliomas may spread to the peritoneum and vice versa. Because DMM is often difficult to diagnose by histologic examination, it is important to distinguish pleural metastatic lesions from primary tumors of the lung, gastrointestinal tract, pancreas and ovary with appropriate diagnostic tests.

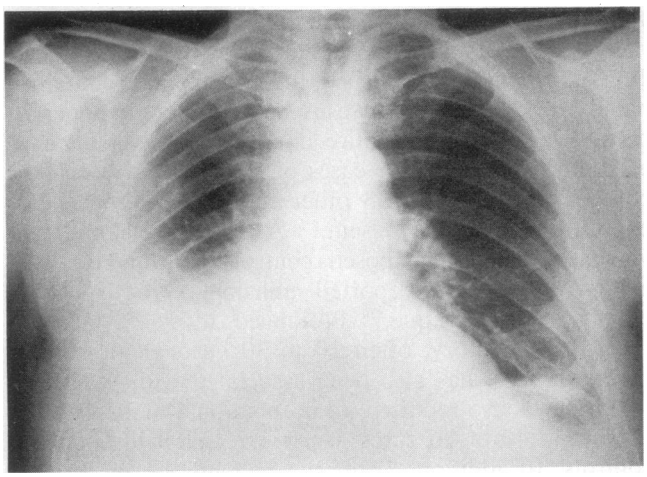

Figure 1.—X-ray film of the chest showing right pleural effusion and diffuse malignant mesothelioma in a 63-year-old brickmaker who made bricks containing asbestos from 1942 to 1955.

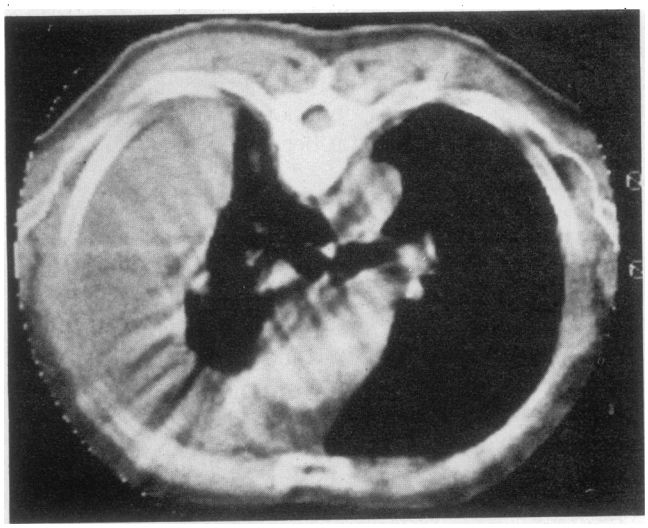

Figure 2.—Computerized axial tomographic scan from the same patient as in Figure 1 illustrating tumor in the right thoracic cavity.

X-ray studies of the chest (Figure 1) usually reveal a large pleural effusion accompanied by a lobulated pleural density encasing the entire lung.[56,57] Pleural plaques may be noted enface, in profile along the lateral chest wall and atop the diaphragm. They are frequently calcified. Parenchymal asbestosis cannot always be identified on x-ray films, and is more noticeable in the uninvolved lung. Computerized axial tomography (Figure 2) may show the thickened tumor along the chest wall.[12]

Microscopic examination of the sputum rarely shows malignant cells, unless the tumor has invaded the lung parenchyma. Asbestos bodies are sometimes seen in the sputum or lung parenchyma, and in rare cases in the tumor.[58] Cytologic examination of pleural fluid is useful in a half to two thirds of the cases, depending on the experience of the cytologist; however, distinguishing DMM from metastatic adenocarcinoma or benign inflammatory conditions is often difficult. Roberts and Campbell successfully identified 8 of 14 and Butler and Berry 25 of 26 cases of DMM by the presence of malignant mesothelial cells in the pleural fluid.[59,60] Finding cell aggregates with a collagen core in the pleural fluid assists in differentiating DMM from metastatic carcinoma.[61] Electron microscopy of malignant and atypical mesothelial cells may also be useful.[62]

Malignant mesothelioma may concentrate gallium 67, and scanning with this radioisotope may prove useful in the future in differentiating malignant from benign pleural disease.[63] The scan may be useful in staging the disease at the onset of treatment and monitoring for recurrences during therapy.[64]

Examination of a pleural biopsy specimen is necessary for accurate diagnosis, even if cytologic findings are abnormal. Accurate diagnosis of DMM requires large biopsy specimens because there is considerable variability among areas of the same tumor, often with large amounts of intervening fibrous tissue. An open pleural biopsy is recommended, which can be combined with a procedure to remove tumor mass. Thoracoscopy with biopsy of pleural masses is an effective, specific technique that may supplant open biopsy, especially if the surgeon has experience with this procedure. DMM has been reported to grow into incisional sites, even needle biopsy tracks, causing considerable pain, but this is uncommon.

Pathologic Diagnosis

Primary neoplasms of the pleura were first recognized by Wagner in 1870, and Klemperer and Rabin popularized the term "mesothelioma" in 1932.[65,66] They also described two types of mesothelioma: the benign, solitary mesothelioma and DMM. The benign, solitary

type remains localized, although it may grow large and compress neighboring thoracic structures. It seldom has signs of malignancy and no association of this type of mesothelioma with asbestos exposure has been found to date.[67] The predominantly fibrous nature of the tumor has promoted the name "localized fibrous tumor of pleura"; it appears to arise from fibroblasts and other connective tissue elements in the areolar submesothelial cell layers of the pleura.[68] By contrast, DMM arises from either the pluripotential mesothelial cell or the primitive submesothelial mesenchymal cell, which retains the ability to form epithelial or connective tissue elements.

On gross examination, numerous tumor nodules may be noted, and in advanced cases the tumor bulk has a hard, woodlike consistency. On histologic examination variation among areas of the same tumor is characteristic.[69] In a series of 382 cases of DMM, 54.5 percent were epithelial, 21.5 percent sarcomatous and 25 percent mixed (biphasic).[70] Mesothelioma tumor boards have been formed in the United States, Canada, South Africa and Western Europe to assist in accurate pathologic diagnosis.[71]

The ultrastructure of mesotheliomas is composed of mesothelial cells joined by infrequent desmosomes. The cells are covered with irregular microvilli that may be seen within crypts in the cytoplasm. The cells have a prominent, dilated, rough endoplasmic reticulum containing basement-membrane-like material. Collagen formation by tumor cells may be prominent. The cells are embedded in a matrix of basement-membrane-like material containing fibrillar elements.[72-75]

Histochemical techniques may be valuable in confirming the diagnosis. Acid mucopolysaccharide (for example, hyaluronic acid) is detected in more than 75 percent of well-differentiated DMM, but is found less frequently in the more undifferentiated forms.[76-80] The Hale colloidal iron or alcian blue stain may show the presence of cytoplasmic vacuoles containing hyaluronic acid. Following hyaluronic acid digestion, the colloidal iron stain will be negative. The PAS and mucicarmine stains are negative for hyaluronic acid, but are positive for mucin in mucin-producing adenocarcinomas. Carcinoembryonic antigen is usually present in tumors of bronchial epithelial origin and absent in mesotheliomas.[81]

Therapy and Prognosis

Individual therapeutic modalities have had little or no success; therefore, the treatment of DMM is best approached by a combined regimen of pleurectomy, followed by radiation therapy, chemotherapy and possibly immunotherapy.[82-84] Chahinian and Holland have recently reviewed the available therapies.[85] Borow and associates reported a series of 72 cases from Somerville, New Jersey, site of a large asbestos factory.[86] The median survival was 15 months. One patient lived 2½ years, but none of the others survived more than 19 months.

Chahinian and co-workers prospectively evaluated 69 patients from 1974 to 1980, finding that several factors correlated with survival: patients whose tumors were in the pleura survived twice as long as those with peritoneal tumors; survival for patients with the epithelial type was longer than for those with biphasic or fibrosarcomatous types of tumors. Those younger than 65 years, those who respond well to chemotherapy and those who had had a previous surgical resection all survived longer.[87] The median survival was 12.1 months for all cases. Radical pleural resection resulted in 18 months median survival in 6 cases, and 7 of 28 patients with pleural mesothelioma responded to administration of doxorubicin and 5-azacytidine, achieving a median survival of 22.2 months from first treatment.

Immunotherapy may have a role in longer survival, because depressed T-cell function has been observed in some but not all patients.[88,89] In nine cases of DMM, the percentage and actual number of T-lymphocytes were reduced, and the response to the synthetic mitogen phytohemagglutinin was also impaired.[88] Using microcytotoxicity methods, Embleton and co-workers detected little or no tumor-directed cell-mediated immunity against cell cultures from pleural effusions of patients with malignant mesothelioma.[90] In a case report, a patient who had an intact immunological system as measured by lymphocyte surface markers and function values was alive seven years after diagnosis.[91]

Differences in Risk Based on Asbestos Fiber Type and Occupation

A gradation of DMM risk based upon type of asbestos fiber (crocidolite greater than amosite greater than chrysotile) has been claimed.[92,93] This variation may be due to physical properties of the fiber; for example, surface properties, aspect ratio, durability or its pulmonary deposition and retention. Timbrell and colleagues have suggested that the reason most cases of DMM in South Africa have come from the northwest Cape Province crocidolite fields is due to the thin fibers with high aspect ratios (length to width) that are found there.[94] Workers who manufactured gas masks from crocidolite during World War II have had a 16-percent mortality due to DMM, while Elmes found only one case among those who used chrysotile for gas mask manufacture.[95-98] Selikoff's group has reported an increased DMM mortality among workers in an asbestos factory using only amosite.[99] Exposure to tremolite in the whitewash or stucco of homes in Turkey has been associated with DMM.[100] DMM has only rarely been reported among Quebec asbestos miners and millers; for example, McDonald has found only 11 cases for a death rate of less than 0.3 percent.[18] The relative risk for DMM is greater in factories using chrysotile fiber than in chrysotile mines; and factories using both chrysotile and amphibole fibers have an even higher risk.[101] Some investigators have suggested a fiber-fiber synergistic action as the cause of DMM.[102] Fibrous erionite (a zeolite aluminum silicate) may interact with asbestos (tremolite, chrysotile) in natural deposits in Cappadocia, Turkey, to cause the high DMM rates found there.[103,104] The differences in mesothelioma occurrence

are much greater for different asbestos fiber types than for different types of work.

Tissue Analysis for Fiber

Both lung and pleural tissue specimens have recently been studied with a variety of techniques to isolate, quantitate and identify fibers. Lung specimens have contained a preponderance of amphiboles with little chrysotile found, even in known cases of mixed or predominantly chrysotile exposures.[18] Magnesium is leached from chrysotile, and chrysotile may either dissolve in tissue or be preferentially cleared from the lung.[105] Most fibers found in pulmonary tissue are less than 6 μm in length, and most chrysotile fibers are less than 2 μm long and 0.125 μm in diameter. Only a small proportion are long fibers, with amosite and crocidolite being predominant. The fate of fibers in the lung depends on their size, with the clearance of short, single fibers being much more rapid than that of long fibers in bundles.

Of great interest is the comparison of fiber types and lengths found in lung and parietal pleura. In 29 cases, Sebastien and co-workers isolated predominantly short chrysotile from the parietal pleura, whereas amphibole fibers were the predominant material (mean 56 percent) found in the lung.[106] However, this group did find short chrysotile fibers in the peripheral areas of the lung instead of the amphibole fibers found in central areas.[107] LeBouffant has also suggested a selective concentration of short (less than 5 μm) chrysotile in pleural tissue in contrast to the long amphibole fibers found in lung tissue from patients suffering from mesothelioma.[108]

When Jones and associates studied lung tissue from 86 confirmed cases of DMM, they found amosite and crocidolite to be about ten times more common than in controls.[109] Chrysotile was the same in both cases and controls, and in 30 cases there was no chrysotile. It would be interesting to study uninvolved parietal pleura from such a series for fibers. McDonald has corroborated these findings in 37 matched pairs of DMM and controls from North America.[18] Gylseth and colleagues did fiber counts in 15 cases of DMM, finding a range of 2 million to 490 million fibers per gram of lung tissue.[110] They found the median lung fiber concentration to be 18 times higher than in a reference group and found fibers in 14 patients with pleural plaques to be 4 times higher than in the same reference group.

Experimental Carcinogenesis

Animal studies using several species and different routes of exposure have produced DMM using chrysotile, crocidolite, anthophyllite and amosite asbestos. Wagner and co-workers reported 11 mesotheliomas occurring after inhalation experiments in rats (four from crocidolite, four from Canadian chrysotile, two from anthophyllite and one from amosite).[111] Roe and associates noted mesotheliomas in mice after injecting them subcutaneously with asbestos fibers.[112] Smith and co-workers induced mesotheliomas in hamsters after intrapleural injection of amosite and chrysotile asbestos.[113] Stanton and colleagues applied amosite, chrysotile and crocidolite asbestos on fibrous glass pledgets to the pleura in rats, obtaining 58 percent to 75 percent incidences of pleural mesothelioma.[114] Wagner inoculated rats intrapleurally with asbestos and other materials producing similar results.[115] Davis studied the histogenesis of mesothelioma resulting from intraperitoneal injection of crocidolite into rats and mice.[116] Many small, pedunculated nodules were noted on visceral surfaces during the early stage. Later, some nodules became large, but most coalesced into a uniform sheet. Berry and Wagner found a larger relative risk in older rats compared with younger rats for DMM when the pleural cavities were injected with crocidolite.[117] Short asbestos fibers have also been found to cause DMM in animal experiments.[118]

Stanton and Wrench have postulated that fine, long, durable fibers correlated best with carcinogenesis using the nonphysiologic technique of pleural implantation.[119] They implanted various fiber sizes and types into the pleural cavity of rats to observe the incidence of DMM. Four types of asbestos, fibrous glass, aluminum oxide, silicon carbide and potassium titanate all produced pleural mesothelioma. He stated that fibers smaller than 0.25 μm in diameter and longer than 8 μm were uncompromised by phagocytic activity, while those considerably shorter or longer were either ingested or sequestered by adherent phagocytes.

Conclusions

DMM appears to be caused by durable fibers with high aspect ratios (length to width). Thin fibers with a diameter less than 1 μm and a length of more than 10 μm appear to be associated with the disease, but many short fibers may induce a tumor as easily as a few long fibers.[118] Amphibole rather than chrysotile fibers are retained in lung tissue, but DMM has the highest relative risk among asbestos insulators in the United States, who are exposed predominantly to chrysotile. Surface properties and fiber (or other substance) interaction may be important. Fiber transport, translocation and retention may be necessary for specific fiber types and sizes to reveal a carcinogenic response. Systemic changes (deranged immune system, affected chromosomes) may identify those at risk or susceptible to the tumor. Treatment has had little success so that understanding the mechanisms of the disease and prevention are likely to be more productive from the public health perspective.

Signs and symptoms of pleural DMM are chest pain, cough and dyspnea, usually with an effusion that can be identified on a chest radiograph. The effusion is an exudate, and cytologic studies are usually nondiagnostic. Open peural biopsy or thoracoscopy are necessary for a diagnosis by histologic techniques. A computerized axial tomographic scan revealing lobulated or encasing tumor and a positive scan using gallium citrate Ga 67 are useful adjunctive tests, especially for determining the extent of tumor involvement. Pleural plaques, per se, do not connote additional risk for DMM beyond the asbestos exposure, although future epidemiologic studies may modify this statement. People with

past asbestos exposure need to be monitored annually for DMM, as well as malignant lesions of other sites, and asbestosis.

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Medical Practice Questions

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Viral/Bacterial Vaccines in the Treatment of Arthritis

QUESTION:

Are there instances in which it is accepted medical practice to administer viral or bacterial vaccines for the treatment of arthritis? If so, please enumerate.

OPINION:

In the opinion of the Advisory Panels of Internal Medicine, Orthopedics and Preventive Medicine and Public Health, there is no new clinical evidence to validate the administration of viral or bacterial vaccines as a treatment for arthritis. The use of such vaccines for this purpose is not acceptable medical practice.